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RESEARCH ARTICLE

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Serum amyloid a, C-reactive protein, and procalcitonin levels in children with *Mycoplasma pneumoniae* infection

Yuanyuan Jiang[1] | **Wenyang Wang**[1] | **Zhijun Zhang**[1] | **Xianfen Ma**[1] | **Yanyan Sang**[1] | **Jin Wang**[1] | **Guoxiang Xu**[2,3] | **Qiang Feng**[1] | **Shuping Zhao**[1]

[1]Department of Clinical Laboratory, Taian City Central Hospital, Shandong, China

[2]Shanghai Upper Bio Tech Pharma Co., Ltd, Shanghai, China

[3]Shanghai Engineering Research Center of iPOCT Medicine, Shanghai, China

Correspondence
Shuping Zhao, Department of Clinical Laboratory, Taian City Central Hospital, No. 29, Longtan Road, Taishan District, Taian 271000, Shandong Province, China.
Email: dczhshp8@126.com

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Abstract

Background: *Mycoplasma pneumoniae* (MP) is a common pathogen of community-acquired pneumonia in children. In the present study, serum amyloid A (SAA), C-reactive protein (CRP), and procalcitonin (PCT) levels in children with MP infection were analyzed and the differential diagnoses of MP evaluated.

Methods: The study included 152 children with MP infection hospitalized in Tai'an Central Hospital in Shandong Province and 50 healthy children as controls. SAA, CRP, and PCT, as well as serum immunoglobulins and T lymphocyte subsets were analyzed during the acute and convalescent phases. Among the MP-infected children, 30 cases were selected to monitor the SAA, immunoglobulins, and T lymphocyte subset levels for a week.

Results: The SAA, CRP, PCT, IgA, and IgM levels were significantly higher in the MP-infected group than in the control group ($F_{(SAA)} = 83.91$, $p < 0.05$; $F_{(CRP)} = 40.79$, $p < 0.05$; $F_{(PCT)} = 60.58$, $p < 0.05$; $F_{(IgA)} = 43.45$, $p < 0.05$; $F_{(IgM)} = 233.88$, $p < 0.05$). In addition, the levels of these factors were significantly higher in the acute phase than in the convalescent phase ($p < 0.05$). However, significant difference was not observed in the IgG level between these two groups ($p > 0.05$). The $CD3^+$ and $CD4^+$ levels in the MP-infected group were lower than in the control group ($F_{(CD3+)}= 60.58$, $P < 0.05$; $F_{(CD4+)} = 89.05$, $p < 0.05$), and the $CD8^+$ level was higher than in the control group ($F_{(CD8+)}= 96.96$, $p < 0.05$). The $CD3^+$, $CD4^+$, and $CD8^+$ levels were significantly different between the acute phase and the convalescent phase ($CD3^+$: acute phase *vs*. convalescent phase, $q = 2.79$, $p < 0.05$; $CD4^+$: acute phase *vs*. convalescent phase, $q = 2.83$, $p < 0.05$; $CD8^+$: acute phase *vs*. convalescent phase, $q = 3.15$, $p < 0.05$). The changes in serum SAA levels in the MP-infected group positively correlated with the changes in IgA, IgM, and $CD8^+$ levels and negatively correlated with $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$.

Conclusion: SAA, CRP, and PCT were specific markers for diagnosing early MP infection in children. These findings are important in the differential diagnosis of MP infection and clinical guidance for MP treatment.

Yuanyuan Jiang and Wenyang Wang contributed equally to this work.

KEYWORDS
C-reactive protein, *Mycoplasma pneumoniae*, peripheral blood T lymphocyte subsets, serum amyloid A, serum immunoglobulin

1 | INTRODUCTION

Mycoplasma pneumoniae (MP) is a common pathogen of community-acquired pneumonia in children.[1] When MP infection occurs in infants and young children, it causes inflammation of respiratory tracts and immune system disorders[2] such as arthritis, myocarditis, and thrombosis. Multiple organ failure might occur in severe cases.[3] Numerous diagnostic methods of MP infection have been developed, and isolation and culture of MP are one of the most reliable methods; however, the procedure is time-consuming. PCR is another method with good specificity and sensitivity but requires specialized equipment. Currently, the clinical diagnosis of MP infection is mainly based on MP serological antibodies. In the serological diagnosis method, a serum test is performed during the acute and recovery phases and whether infection is present determined based on obvious changes in antibody titer. In addition, the results are easily affected by the status of pediatric patients with previous infection. Reportedly, some disorder occurs in humoral immunity and cellular immunity in children infected with MP, which is directly proportional to the infection status, indicating the occurrence of MP may be associated with the immune mechanism.[4]

Serum amyloid A (SAA) proteins are normal constituents of blood serum, small, and remarkably well-conserved in mammalian evolution. SAA proteins and C-reactive protein (CRP) are the most prominent members of the acute phase reactants (APR) during which their serum levels rise dramatically after trauma, infection, and other stimulation.[5] The biological functions of SAA are unresolved; however, features are consistent with a prominent role in the primordial host defense. Procalcitonin (PCT) and CRP are commonly used biomarkers; however, their diagnostic advantage for MP infection is unclear.[6] Neeser, OL concluded that elevated CRP/PCT ratio independently predicted MP.[7] However, the combined detection of SAA, CRP, and PCT in the diagnosis of mycoplasma infection has not been reported.

In the present study, the changes in serum SAA, CRP, and PCT levels as well as immune function (serum immunoglobulin levels and peripheral blood T lymphocyte subsets) were analyzed in children with MP infection and the relationship between SAA and immunity investigated. The results will provide a scientific basis for the application of SAA in early diagnosis, evaluation of treatment efficacy, and prognosis of MP infection.

2 | MATERIALS AND METHODS

2.1 | Study subjects

The study was approved by the Ethics Committee of Tai'an Central Hospital (IRB NUMBER: 2018-06-44 IRB, APPROVAL DATE: 7/11/2018) and performed in accordance with the approved guidelines. All patients provided informed consent prior to participation in this study. A total of 152 children infected with MP, who were hospitalized from October 2018 to March 2019, were selected for this study.

The medical records of all patients met the inclusion criteria as described in the 8th edition of Zhu Futang Practical Pediatrics.[8]

2.2 | SAA, CRP, and PCT detection

Venous blood samples of the MP-infected children were collected on the morning after admission (the acute phase) and during the convalescent phase after the patients fasted for at least 8 hr. SAA kits (Cat. No.20180802) and CRP kits (Cat. No. 20180730) were obtained from Upper Bio-TECH Pharma Co. Ltd. (Shanghai, China), and PCT kits were obtained from Guangzhou Wondfo Biotech Co. Ltd. (Guangzhou, China). The same procedure was performed for the healthy children in the control group.

2.3 | Detection of immunoglobulins in serum

The serum levels of immunoglobulins IgG, IgA, and IgM were detected with a Toshiba TBA-120 automatic biochemical analyzer (IgA: Cat. No. ZCNOVT018; IgM: Cat. No. ZCDECN010; IgG: Cat. No. ZCAPRT021; Zhicheng Biological Technology Co. Ltd. Shanghai, China).

2.4 | T lymphocyte $CD3^+$, $CD4^+$, and $CD8^+$ subsets in peripheral blood

Peripheral blood mononuclear cells (PBMCs) were obtained from the MP-infected children; the population of lymphocytes and T cells did not differ between groups. All specific staining antibodies (CD4: Cat. No. 11-0049-80; CD8a: Cat. No.12-0088-42; CD3: Cat. No. MHCD0331; CD45: Cat. No. 25-0459-42; Thermo Fisher Scientific, Inc. Waltham, MA, USA) used to measure the levels of T lymphocyte $CD3^+$, $CD4^+$, and $CD8^+$ subsets are routinely evaluated for effectiveness by the manufacturer and titrated for optimal concentration in our laboratory.

2.5 | Correlation between SAA and immunoglobulins and T lymphocyte subsets

Correlation analysis was conducted using Pearson correlation analysis. Venous blood samples were collected from 30 children with

MP infection from the second morning of admission for 7 consecutive days, and the correlation between SAA, immunoglobulins (IgG, IgA, and IgM), and T lymphocyte subsets ($CD3^+$, $CD4^+$, and $CD8^+$) analyzed.

2.6 | Statistical analyses

Statistical analyses were performed with the SPSS 20.0 software. The percentage and comparison were performed using the chi-squared test. The measurement data were expressed as mean ± standard deviation (SD), and comparison was performed using the *t* test. Welch's *t* test was used when the two samples had unequal variances. $p < 0.05$ was considered statistically significant. The *F* test was used for comparison between multiple groups, and the Cochran *q* test was used for pairwise comparison within a group.

3 | RESULTS

3.1 | Demographic and clinical features and the laboratory findings

The 202 patients enrolled in our study, of whom 95 (47.03%) were male and 107 (52.97%) were female. The acute-phase group had higher SAA ($p < 0.05$), CRP ($p < 0.05$), PCT ($p < 0.05$), IgA ($p < 0.01$), and IgM ($p < 0.01$) levels and lower $CD3^+$ ($p < 0.05$), $CD4^+$ ($p < 0.05$) levels. Further analysis of the data reveals the serum SAA, CRP, PCT, IgA and IgM levels in patients in the convalescent phase were statistically significantly lower than in the acute phase ($F_{(SAA)} = 83.91, p < 0.05$; $F_{(CRP)} = 40.79, p < 0.05$; $F_{(PCT)} = 60.58, p < 0.05$). The $CD3^+$, $CD4^+$, and $CD8^+$ levels in children with MP infection were statistically significantly different between the acute and convalescent phases ($p < 0.05$). Table 1 presents the results obtained from the preliminary analysis of the laboratory findings.

3.2 | SAA levels in the mild and severe groups

In the acute phase, the serum SAA levels differed between the mild and severe groups. As shown in Figure 1, the serum SAA level in the severe group was significantly higher than in the mild group ($p < 0.05$). The serum SAA level in the acute phase can reflect the severity of the disease in children with MP infection.

3.3 | ROC curve analysis of SAA, CRP, and PCT

Figure 2 provides the ROC curve analysis of SAA, CRP, and PCT, the serum SAA cutoff value was 203.56 mg/L (86.7% sensitivity and 83.3% specificity, AUC = 0.924, $p < 0.05$), the serum CRP cutoff value was 32.6 mg/L (80.0% sensitivity and 80.0% specificity, AUC = 0.861, $p < 0.05$), and the serum PCT cutoff value was 1.12 ng/ml (70.0% sensitivity and 73.3% specificity, AUC = 0.779, $p < 0.05$). These results indicated serum SAA, CRP, and PCT levels are useful for the accurate diagnosis of MP infection. AUC of SAA was the highest among the three AUC values, indicating SAA may be the best indicator for the diagnosis of MP infection.

TABLE 1 Demographic and clinical features and laboratory findings of patients

Characteristic	Control ($n = 50$)	Acute phase ($n = 152$)	Convalescent phase ($n = 152$)	*F* value	*p* value
Average age	4.07 ± 2.06	3.67 ± 2.04			0.23
Male	24(48%)	71(46.7%)			0.87
Female	26(52%)	81(53.3%)			
SAA (mg/L)	7.08 ± 1.87	195.76 ± 36.85*	82.56 ± 20.18#		
Square root SAA	2.64 ± 0.36	13.80 ± 3.08	9.02 ± 2.06	83.91	<0.001
CRP (mg/L)	1.35 ± 1.32	25.56 ± 8.25*	13.82 ± 5.57#		
Square root CRP	1.07 ± 0.47	5.07 ± 2.03	3.08 ± 1.12	40.79	<0.001
PCT (ng/ml)	0.15 ± 0.02	0.49 ± 0.05*	0.33 ± 0.09#		
Square root PCT	0.35 ± 0.06	0.68 ± 0.04	0.56 ± 0.08	60.58	<0.001
IgA (g/L)	0.61 ± 0.09	0.76 ± 0.11*	0.67 ± 0.12#	43.45	<0.001
IgM (g/L)	0.94 ± 0.10	1.37 ± 0.15*	1.15 ± 0.12#	233.879	<0.001
IgG (g/L)	7.25 ± 0.29	7.11 ± 0.28	7.04 ± 0.23		0.12
Average $CD3^+$ (%)	70.15 ± 5.03	61.43 ± 5.13*	66.45 ± 5.36#	65.54	<0.001
Average $CD4^+$ (%)	48.92 ± 4.23	40.32 ± 4.13*	44.67 ± 4.36#	89.05	<0.001
Average $CD8^+$ (%)	28.43 ± 2.63	34.31 ± 3.13*	30.15 ± 3.02#	96.96	<0.001

*Statistical difference with the control group $p < 0.05$.

#Statistical difference with the Convalescent phase group $p < 0.05$.

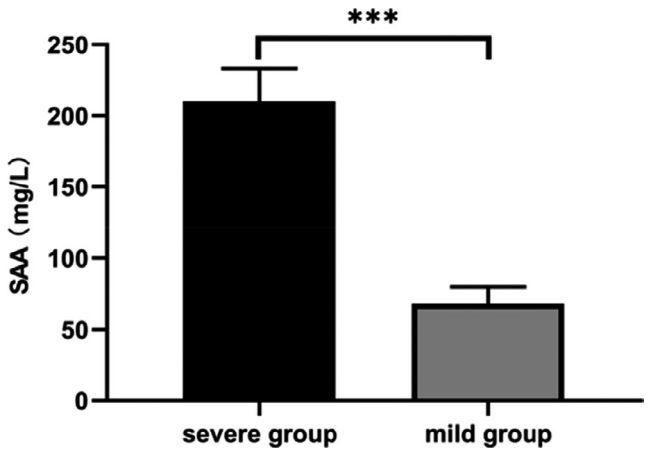

FIGURE 1 Comparison of SAA between mild and severe group in acute phase. The severe group is significantly higher than the mild group, and the difference is statistically significant ($p < 0.05$)

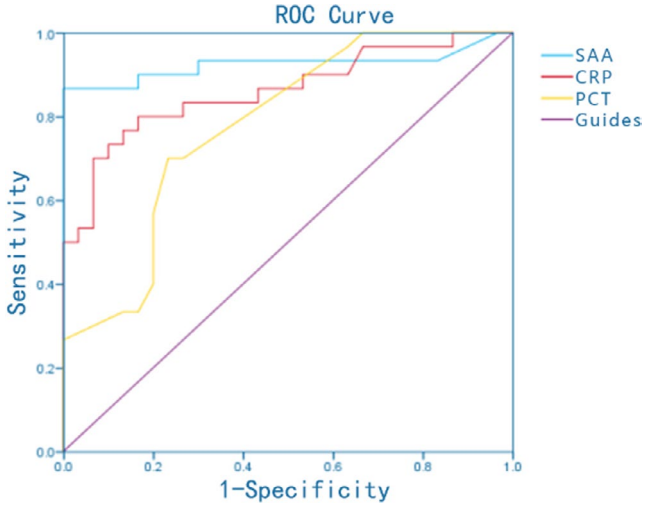

FIGURE 2 ROC curve of SAA, CRP, and PCT in children with MP infection. The serum SAA cutoff point is at 203.56 mg/L (with 86.7% sensitivity and 83.3% specificity, AUC = 0.924, $p < 0.05$); the serum CRP cutoff point is at 32.6 mg/L (with 80.0% sensitivity and 80.0% specificity, AUC = 0.861, $p < 0.05$); the serum PCT cutoff point is at 1.12 ng/ml (with 70.0% sensitivity and 73.3% specificity, AUC = 0.779, $p < 0.05$)

3.4 | Correlation and regression analysis between SAA and various immune status markers

A close correlation existed between SAA and various immune status markers as shown in Table 2. The change in serum SAA level positively correlated with the change in IgA and IgM levels and $CD8^+$ T cells (%) and negatively correlated with the change in $CD3^+$ and $CD4^+$ T cells (%).

3.5 | Changes in SAA, immunoglobulins, and lymphocyte subsets on Day 1 and Day 7 after treatment

The change in trend of serum SAA level and immune status markers is shown in Figures 3 and 4; the change in SAA level positively correlated with IgA and IgM levels and $CD8^+$ T cells (%), which reached the highest on the third and fourth day. Conversely, the change in trend of serum SAA level negatively correlated with $CD4^+$ T cells (%).

4 | DISCUSSION

Isolation of MP from throat swab or sputum culture is considered the gold standard for the diagnosis of MP infection. However, serology is the most frequently used method to diagnose MP infection.[9] In the present study, serum SAA, CRP, and PCT levels were used to diagnose early MP infection in children. The changes in serum SAA levels in the MP-infected group positively correlated with the changes in IgA and IgM levels and $CD8^+$ cells and negatively correlated with $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$. These findings are important in the differential diagnosis of MP infection and clinical guidance for MP treatment.

In the present study, serum CRP levels in children with MP infection were higher in the acute phase than in the convalescent phase, and decreased rapidly after recovery, indicating serum CRP levels can be used to accurately diagnose MP infection. However, multiple logistic regression analysis showed that CRP ≥ 16.5 mg/L was a significant predictor regarding refractory MP pneumonia (MPP) described by Yuanyuan Zhang.[10] In our research, the average CRP level in children infected with MP at the acute stage was 25.69 mg/L, which was consistent with Zhang. The difference between severe mycoplasma infection and mild infection should be investigated in further studies. Similarly, the results showed that serum PCT levels slightly increased in the acute phase and decreased rapidly with the recovery of the disease; the difference between the acute and convalescent phases was statistically significant. In the present study, the AUC ROC of 0.779 for PCT when the MP group was compared with the control group is in agreement with the AUC ROC of 0.75 described by Jereb et al. for typical *versus* atypical pneumonias.[11] Therefore, the change in the serum PCT level is an important indicator of the status of MP infection, which can be used to guide drug applications, evaluate drug efficacy, and improve prognosis. Conversely, the changes in serum SAA level in children with MP have not been previously studied. The present study results showed that serum SAA levels increased rapidly in children with MP infection during the acute phase and declined rapidly with the improvement of the disease; the difference was statistically significant between the acute and convalescent phases. This result indicates after infection with MP, the expression of various inflammatory cytokines increases, subsequently promoting the synthesis and secretion of SAA in the liver. SAA may further deteriorate inflammation in children with MP infection through its pro-inflammatory activity. Therefore, the serum SAA level is closely correlated with immune functions.[12,13]

The comparison of SAA between the MP and control groups showed an AUC ROC of 0.924, indicating that SAA may be the best indicator for the diagnosis of MP infection. Neeser, OL indicated the

TABLE 2 Correlation and regression analysis of SAA, immunoglobulin, and T lymphocyte subsets

Pairwise	Correlation coefficient	*p* value	Regression equation
IgA and SAA	0.9742	0.0002	IgA = 0.3657 + 0.0011 SAA
IgM and SAA	0.9932	< 0.0001	IgM = 0.9938 + 0.0025 SAA
$CD3^+$ and SAA	−0.9491	0.0011	CD3 = 84.17–10.76 lg SAA
$CD4^+$ and SAA	−0.9851	< 0.0001	CD4 = 50.667–0.0522 SAA
$CD8^+$ and SAA	0.9718	0.0003	CD8 = 26.36 + 0.0409 SAA

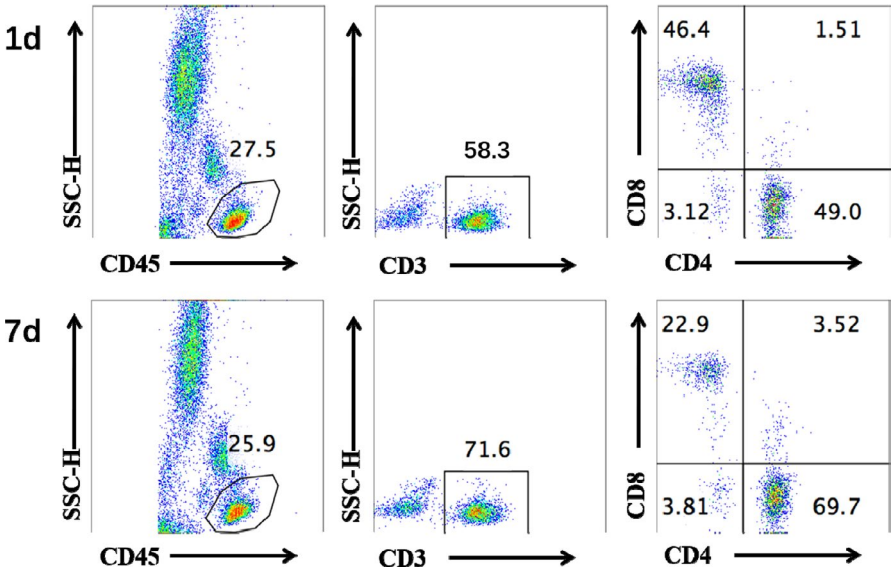

FIGURE 3 Changes in lymphocyte subsets in a child on Day 1 and Day 7 after the treatment. The percentages of T lymphocyte subsets ($CD3^+$, $CD4^+$, and $CD8^+$) of a child with MP infection on the 1st and 7th days have significant changes

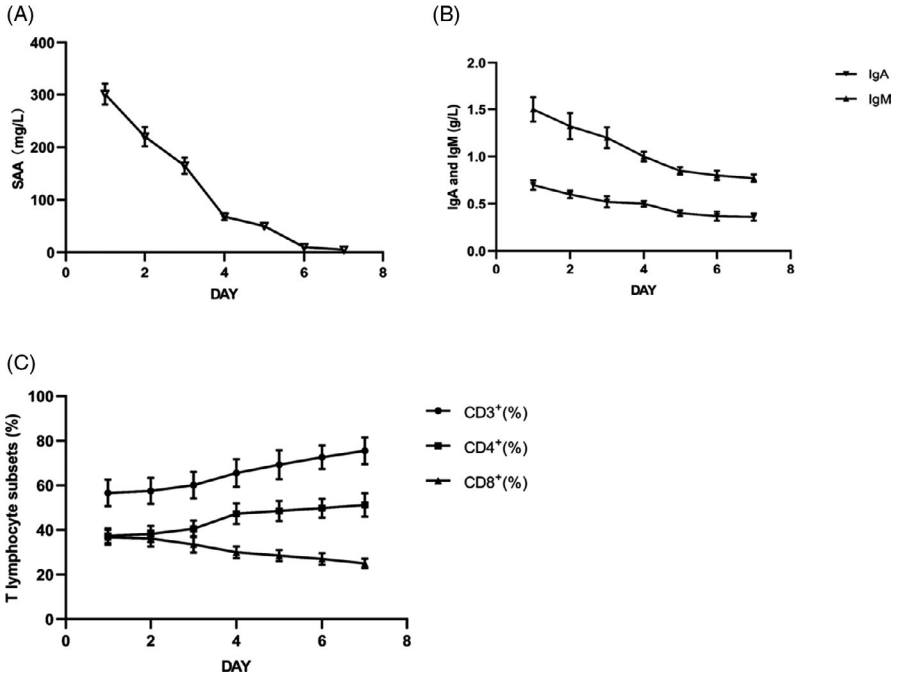

FIGURE 4 Changes in SAA, immunoglobulin, and T lymphocyte subsets. The change in SAA is positively correlated with that of IgA, IgM, and $CD8^+$ T cells (%), which reached the highest on the third and the fourth day. On the contrary, the change trend of SAA is negatively correlated with that of $CD4^+$ T cells (%)

CRP/PCT ratio predicted MP compared with *Streptococcus pneumoniae* (SP) with an AUC ROC of 0.91 and an OR of 15.04 when a cutoff > 400 mg/μg was chosen.[7] In addition, serum SAA level was 203.56 mg/L with 86.7% sensitivity and 83.3% specificity, indicating that SAA is a better indicator than PCT or CRP for accurate diagnosis of MP infection. In summary, the detection of SAA, CRP, and PCT is useful for early diagnosis of MP infection, among which SAA has the highest sensitivity.

In previous studies, changes in T-cell subsets were shown closely associated with the progress of MP infection, and MP can activate polyclonal lymphocytes and deteriorate the internal environment of T lymphocyte subsets,[14] which further disrupts the immune system and affects the proliferation and differentiation of other immune cells. MP activates lymphocytes and mitogens to change the environmental balance within T cells. The activation of T cells can promote the secretion of cytokines which regulate the proliferation and differentiation of immune cells. Transient immunosuppression has been observed in patients with early MP infection.[15] In the present study, the subsets of $CD3^+$ and $CD4^+$ T cells were low and the $CD8^+$ cells significantly elevated in the acute phase, indicating that after MP infection, a large amount of mature T cells are lost, which significantly changes the T-cell ratio. Guo also reported a significantly decreased percentage of $CD3^+$ T cells in bronchoalveolar lavage fluid in children with MPP compared with controls.[16] The severity of the disease is closely correlated with the type of immune disorder, which leads to significantly reduced defense responses and severe tissue damage.[17] In previous studies, decreased $CD4^+$ cells reportedly reduced the production of lymphokines, and decreased $CD4^+$/$CD8^+$ can lead to the weakening of antibody production in B cells, indicating that MP infection is closely associated with humoral immune disorders.[18] Therefore, studying the changes in the immune mechanism of children with MP infection can provide a basis for clinical evaluation and guide treatment plans, which is important for reducing complications and mortality.

Furthermore, in the acute phase of MP infection, IgA and IgM levels were significantly increased and IgG level did not significantly change. Consistent with previous studies,[19] the present study results showed that after MP infection, the lymphocyte subsets and IgG and IgM levels changed to varying degrees. MP infection can inhibit the production of IgG and IgM antibodies secreted by B cells, resulting in changes in the antigen structure of the host cell membrane and causing pathological immune responses. Under normal circumstances, within 2 weeks after MP infection, the IgA and IgM levels increase but IgG levels do not significantly change,[20,21] which is consistent with the results of the present study and may be associated with the course of infection. In general, IgG levels do not significantly increase until 2 weeks after infection, and most of the subjects in this study did not experience more than 2 weeks of illness; thus, the IgG levels did not significantly change during their recovery period. However, the IgG level showed an increasing trend after 2 weeks, indicating temporal changes in IgA, IgM, and IgG levels differ after MP infection. In several studies, the serum IgA, IgM, and IgG levels of critically ill children were significantly higher than in mildly ill children, indicating the humoral immunity becomes increasingly compromised with the progression of MP infection.[2] In several studies, the serum total IgE levels were higher in the atopic patients than in the nonatopic patients with increased IgE levels.[22,23]

In summary, MP infection can cause different disorders in the cellular and humoral immunity. The changes in SAA and immune function were monitored in 30 children with MP infection for 1 week and the change in SAA levels closely correlated with the immune function based on regression analysis. The immunity level can be estimated based on the changes in serum SAA levels. When using serum SAA levels as an indicator, the changes in immunity in children can be monitored and the treatment plan and immunotherapy adjusted in a timely manner. However, the conclusions from this study are limited due to the small sample size. Future studies with larger study cohorts should be conducted to confirm the importance of SAA, CRP, and PCT for the early diagnosis of MP infection. The second limitation concerns the IgE levels that were not measured, which will be addressed in our future research.

5 | CONCLUSION

In conclusion, SAA, CRP, and PCT were shown specific markers for diagnosing early MP infection in children. These findings are important in the differential diagnosis of MP infection and clinical guidance for MP treatment.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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